The Catalase-Peroxidase Gene and Isoniazid Resistance in *M. tuberculosis*.

Douglas B. Young and Ying Zhang
MRC Tuberculosis and Related Infections Unit
Hammersmith Hospital, London, U.K.

Isoniazid (isonicotinic acid hydrazide, INH) was first introduced for treatment of tuberculosis in 1952 and, in combination with rifampicin, it continues to play a central role in current therapeutic regimens. The emergence of INH-resistant isolates was documented in the 1950's and it was noted that these strains often showed alterations in catalase activity. Application of molecular genetic techniques has allowed characterization of the *katG* gene of *M. tuberculosis* which encodes an enzyme with both catalase and peroxidase functions. This enzyme is frequently altered in INH-resistant isolates. Alterations include point mutations and, in a subset of highly resistant strains, deletion of the *katG* gene and adjacent sequences. Analysis of a range of resistant and sensitive isolates demonstrates frequent polymorphisms affecting the *katG* region of the *M. tuberculosis* genome, associated with clusters of direct repeat sequences. Transformation with the wild-type *katG* gene fully restores drug-sensitivity in a range of INH-resistant isolates, demonstrating a key role for the catalase-peroxidase enzyme in drug action. It is possible that *katG* is required to convert INH into an activated intermediate within the bacteria. Understanding of such an interaction may allow design of novel drugs which can bypass the *katG* step and which would retain activity against the INH-resistant isolates.